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Case Report

Venetoclax-Associated Leukocytoclastic Vasculitis: A Rare Case

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Abstract:

Venetoclax, a selective BCL-2 inhibitor, is widely used in combination with hypomethylating agents as first-line therapy for elderly or unfit patients with AML. Although its safety profile is generally well established, rare immune-mediated adverse events have been scarcely reported. Herein, we present a 62-year-old male patient with AML who developed LCV shortly after initiation of venetoclax in combination with azacitidine. On the fourth day of treatment, the patient developed non-blanching, raised hyperemic skin lesions predominantly in the pretibial region. Following discontinuation of venetoclax and initiation of systemic corticosteroid therapy, the lesions regressed completely. The patient was subsequently treated with azacitidine monotherapy without recurrence of vasculitic manifestations and achieved hematologic remission. To the best of our knowledge, this is the first reported case of venetoclax-associated leukocytoclastic vasculitis. This case highlights the importance of considering vasculitis in the differential diagnosis of early-onset cutaneous lesions during venetoclax therapy.

Key words: venetoclax; vasculitis; acute myeloid leukemia

Introduction

Acute myeloid leukemia (AML) is the most common acute leukemia in adults, accounting for approximately 1% of all adult malignancies and nearly 2% of cancer-related mortality. The median age at diagnosis is approximately 68 years, with a marked increase in incidence with advancing age [1]. In elderly patients or in those who are unfit for conventional intensive chemotherapy regimens containing cytarabine, the combination of the hypomethylating agent azacitidine and the BCL-2 inhibitor venetoclax has emerged as an effective treatment option and has become one of the standard first-line therapeutic approaches in this patient population[2]. Venetoclax selectively binds to the antiapoptotic BCL-2 protein, leading to the release of proapoptotic proteins and thereby reactivating apoptosis in tumor cells through the intrinsic apoptotic pathway. Due to the associated risk of tumor lysis syndrome, venetoclax is administered using a dose ramp-up protocol [3,4]. During venetoclax treatment, non-specific adverse effects such as diarrhea, nausea, and fatigue are relatively uncommon, whereas the most frequently reported adverse events—both with monotherapy and in combination with hypomethylating agents or cytarabine—are cytopenias (particularly neutropenia and thrombocytopenia) and infections [5]. Herein, we report an AML case complicated by leukocytoclastic vasculitis (LCV), a rare adverse event potentially associated with venetoclax treatment, and review the possible etiopathogenetic mechanisms in light of the literature

Case Presentation

A 62-year-old male patient presented with complaints of dyspnea, fatigue, and fever. His general condition was fair, and vital signs were as follows: arterial blood pressure 110/70 mmHg, heart rate 92 beats/min, and body temperature 38.1 °C. Physical examination revealed no pathological findings other than conjunctival pallor. Laboratory evaluation demonstrated pancytopenia on complete blood count (WBC: 1,450/µL, neutrophils: 350/µL, hemoglobin: 7.7 g/dL, platelets: 62,000/µL). Serum biochemistry showed elevated C-reactive protein (195.3 mg/L) and procalcitonin (14.7 ng/mL) levels. Electrolyte levels, renal function tests, transaminases, and basic coagulation parameters were within normal limits. Peripheral blood smear revealed hypolobulated neutrophils, anisocytosis and hypochromia in erythrocytes, and approximately 6–7 platelets per high-power field. The patient was hospitalized with a preliminary diagnosis of febrile neutropenia for etiological evaluation. After obtaining blood cultures, empiric piperacillin/tazobactam therapy (4 × 4.5 g) was initiated. As no recurrent fever was observed during follow-up, blood cultures remained negative, and no infectious focus was identified on clinical evaluation, antibiotic therapy was discontinued on day 10. Due to persistent cytopenias, bone marrow aspiration and biopsy were performed. The bone marrow was hypercellular with a blast percentage of 18%, accompanied by dysmegakaryopoiesis (>10%) and dyserythropoiesis (>10%). Molecular analysis using next-generation sequencing (NGS) revealed mutations in *TP53*, *SF3B1*, and *EZH2* genes, with allele fractions of 70%, 37%, and 32%, respectively. Based on these findings, the patient was diagnosed with acute myeloid leukemia.

Considering the patient's age (>60 years) and history of chronic obstructive pulmonary disease, he was deemed unfit for conventional intensive chemotherapy, and combination therapy with azacitidine (75 mg/m², days 1–7, every 28 days) and venetoclax (400 mg/day) was planned. On the fourth day of treatment, hyperemic skin lesions that were raised, non-blanching, and showed a tendency to coalesce developed, being widespread in the pretibial area and milder on the back, with progression over several days (Figure 1A). Suspecting a drug-related reaction, treatment was discontinued. Following punch biopsy, methylprednisolone (1 mg/kg/day) was initiated. On day 10 of steroid therapy, marked regression and fading of the skin lesions were observed (Figure 1B).

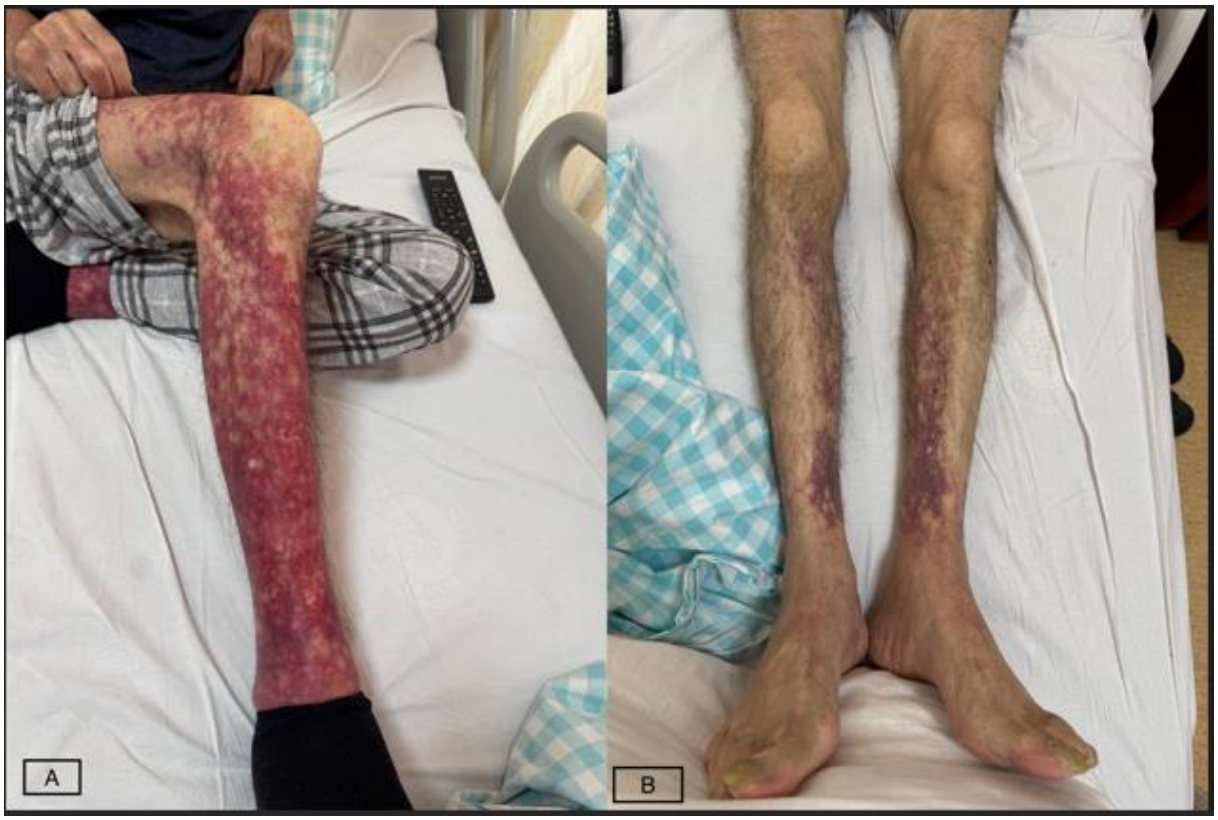

Figure 1: (A) Non-blanching, raised hyperemic pretibial skin lesions observed on day 4 of treatment, **(B)** On day 10 of steroid therapy.

Skin biopsy revealed dense neutrophilic infiltrates surrounding vascular structures in the dermis, consistent with leukocytoclastic vasculitis (Figure 2).

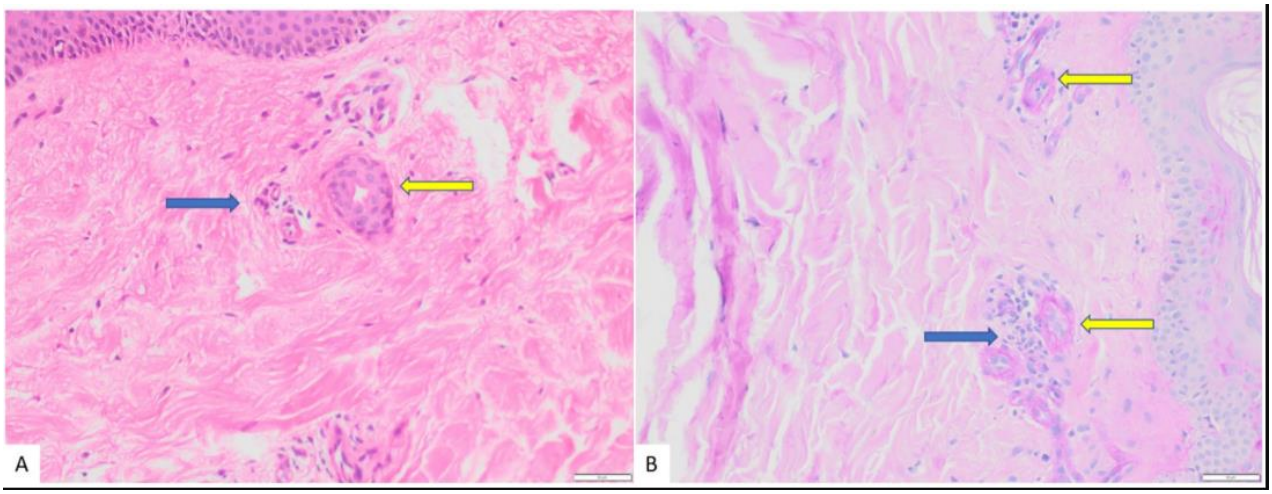

Figure 2: Perivascular mononuclear inflammatory infiltrate with neutrophils (blue arrow) and endothelial swelling of the vessels (yellow arrows). **(A)** Hematoxylen&Eosin, 200x, **(B)** PAS, 200x

During etiological evaluation, antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), cryoglobulin, and viral serological tests were all negative. After achieving clinical improvement, steroid therapy was gradually tapered and discontinued over four weeks. Treatment was continued with azacitidine monotherapy. Given the risk of recurrence, venetoclax was not reintroduced in subsequent cycles, and no

vasculitis-like skin lesions developed during follow-up. The patient is currently in the sixth month of azacitidine therapy and is being followed in hematologic remission.

Discussion

LCV may occur in the setting of hematologic malignancies either through paraneoplastic mechanisms related to the underlying disease itself or secondary to chemotherapeutic and targeted agents [6,7]. The absence of distinctive findings in clinical features as well as coagulation, viral, and serological tests allowed the exclusion of conditions that may cause similar skin lesions, such as infection, autoimmune diseases, and thrombotic microangiopathy. The diagnosis of LCV was further confirmed by pathological examination. Given the rapid onset of vasculitic findings shortly after the initiation of venetoclax, the clinical picture was considered to be associated with venetoclax therapy. The regression of lesions following discontinuation of venetoclax and initiation of steroid treatment, along with the absence of recurrence under azacitidine monotherapy, further supports this association. Although LCV typically develops within 7–10 days following drug exposure, earlier or delayed onset has been reported in chemotherapy-related cases. Rajer et al. described a case that developed on day 22 of carboplatin treatment, whereas Lunge reported an AML patient who developed LCV presenting with erythematous plaques on the second day of azacitidine cure [8,9]. In our case, vasculitis developed relatively early, on the fourth day of venetoclax treatment. In studies demonstrating the efficacy of venetoclax in AML, the most frequently reported adverse events, apart from hematologic abnormalities and febrile neutropenia, are non-specific gastrointestinal side effects such as decreased appetite, nausea, vomiting, and constipation. In addition, hypokalemia, peripheral edema, and atrial fibrillation have also been reported [2,5]. Most of these adverse events are of grade 1–2 severity. A review of the literature revealed no previously reported cases of vasculitis associated with venetoclax. In this regard, our case represents a unique and noteworthy contribution to the existing literature Venetoclax is a potent targeted agent that induces cellular apoptosis through BCL-2 inhibition [3]. It may be hypothesized that increased apoptosis and antigen release contribute to an increase in circulating immune complexes, thereby triggering vasculitic processes through a type III hypersensitivity mechanism. In addition, apoptosis of endothelial cells and alterations in cytokine release may predispose to the development of microvascular inflammation [6]. However, these mechanisms have not yet been clearly elucidated in clinical studies. In conclusion, early-onset cutaneous lesions in AML patients receiving venetoclax therapy should not be attributed solely to infection or thrombocytopenia-related bleeding but should also be carefully evaluated for leukocytoclastic vasculitis. Early recognition and appropriate management are essential to prevent unnecessary treatment interruptions and to avoid potential systemic involvement.

Conflict of Interest

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Data Availability Statement

The datasets generated and/or analyzed during the current study, as well as the related materials and software applications, are available from the corresponding author on reasonable request. All data comply with field standards.

Declaration of Helsinki

This study was performed in line with the principles of the 1964 Declaration of Helsinki and its later amendments.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) for language editing and improvement of readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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